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MEASLES IMMUNIZATION[1]

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It is tempting to begin by saying that we have learned more about measles and its causative virus in the past decade than in the 196 years that intervened between Francis Home's first attempt at immunization in 1758 (1) in Edinburgh and 1954 when Enders and Peebles (2) adapted the virus to tissue cultures of human-kidney cells. As usual, time and space do not permit us to dwell upon the past, but it is well to bear in mind that here, as elsewhere, we more often stand upon a predecessor's shoulders than upon the ground. Yet, one cannot help but be excited by the fact that, within 9 years after the virus definitely had been isolated, at least two different vaccines became commercially available to children in this country and elsewhere. This is even more impressive when one considers the increased (and increasing) hurdles that, very properly, have been interposed between the research laboratory and the ultimate recipient of a vaccine.

Of the two available vaccines, one, attenuated, live virus (4), and the other, inactivated, concentrated, and alum-containing (14), my colleagues and I have had more direct experience with the latter (3). I trust that this brief summary will help to clarify some of the confusion that has arisen over the relative merits of, and the indications for, the two immunizing systems. Both vaccines, incidentally, are derived from the original Edmonston strain which Dr. Enders isolated in Boston. Basically, two live virus vaccines have been studied, although only one is currently available as a licensed product. This is an attenuated strain of Edmonston virus prepared in chick-embryo tissue cultures. The second (7), prepared in canine renal tissue cultures, is not yet on the market but probably will become available in the near future. An additional variant, labeled "further attenuated," is also under study (6, 10), but not yet licensed.

One of the major problems in the production of live virus vaccine has been that the government has insisted that this be produced in egg material that has been demonstrated to be free from the avian leucosis virus complex. This very proper restriction poses some practical problems which can be overcome, although not without some difficulty.

The inactivated virus vaccine that we have used has been made from virus grown in primary rhesus monkey-kidney cell cultures. Here, too, all of the usual precautions concerning the presence of SV_{40} virus, etc., had to be taken for the vaccine to have been cleared for general use.

Some 6 to 8 days after the subcutaneous injection of live vaccine virus, fever (8) will be noted in approximately 80% of susceptible recipients. About half of such children will have temperatures of 103 F or more. Rash occurs in about half, and Koplik's spots, cough, conjunctivitis, and coryza in lesser numbers. Electroencephalogram changes and convulsions have been unusual in this country, but seizures have been reported in as many as 2% of vaccinees in some overseas studies (8). Reactions can be reduced in one of two ways. The first is by the administration of rather precise amounts of γ-globulin at the same time that the virus vaccine is injected. (This is a patented procedure!) The γ-globulin must be injected in a site other than the one in which the vaccine virus is introduced. Best results are obtained when the two injections are administered almost simultaneously. If the γ-globulin inoculation precedes the vaccine virus, one may not get a "take." One set of such injections, properly administered, will result in the serological conversion of almost 100% of susceptibles (5).

The second way in which a reduction of the reaction rate has been sought is by the further attenuation of the virus through additional passages in tissue culture. Such a vaccine (6), currently under study, when administered with-

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out γ-globulin results in a reaction rate similar to that observed with the regular virus vaccine plus γ-globulin. The conversion rates here, too, are high and satisfactory, but the antibody decay rates (not necessarily the same as immunity) require additional observation before any conclusions can be drawn as to the persistence of the protection provided by this modified vaccine.

The absolute contraindications for the use of live virus vaccine appear to be age less than 8 months, leukemia, and egg hypersensitivity (if the vaccine is produced in egg tissues). It probably is well not to administer it to pregnant women, especially in the first trimester. It has been reported (9, 11) that measles, γ-globulin modified measles, and vaccine virus measles may depress the tuberculin reaction in children with tuberculosis. Whether this means that such children should not receive live virus vaccine is not clear. There probably is no contraindication, at least if the patient is receiving antituberculous chemotherapy.

Live virus vaccine never should be given to anyone who has received γ-globulin for any purpose during the preceding 6 weeks, at least. It probably ought not to be administered to children with malignancies or to those receiving steroids or immunity-interfering substances. Aqueous vaccine must be stored in the frozen state. If lyophilized, it may be stored in an ordinary refrigerator for a long period of time.

In the case of the inactivated virus vaccine [It should be understood that the preparation being discussed here is not the inadequate material employed (4, 13) as a placebo and discounted entirely by Weibel and Stokes (16). That vaccine is not available for general use and continued reference to it merely clouds the issue.], there do not appear to be any contraindications for its use. (The exception would be egg-derived vaccine in egg-sensitive children.) It is indicated, at the very least, in those situations where live virus is contraindicated, but this is a somewhat negative line of reasoning. There are very real, positive attributes of this vaccine. It can be mixed with other antigens, such as polio (15) or diphtheria-pertussis-tetanus (DPT), without interfering with its antibody-producing capacity. Immunization may be initiated rather early in infancy, and reactions are negligible.

In our original study (3), we found that neutralizing or hemagglutination inhibition (HI) antibodies resulting from inactivated virus vaccine tended to disappear almost completely within 6 months. Subsequent challenge with live virus vaccine without γ-globulin produced a very prompt increase in antibodies to levels similar to those observed after natural infection. This occurred in the absence of clinical evidence of disease. Thus, it was shown early in its study, and supported since by our own work as well as by that of others, that immunization with inactivated virus vaccine does not prevent subsequent infection with either "wild" or vaccine viruses. With the latter, there is usually no disease, whereas with the former there may be none or a very mild, modified illness. In both instances, solid immunity follows.

Additional, larger-scale studies (8) have been conducted in which live virus vaccine was used in conjunction with inactivated virus vaccine. In general, the results have indicated that two or three doses of inactivated virus vaccine prevent the reactions which follow the exhibition of live virus vaccine without γ-globulin. In a very interesting and importnt study conducted recently by Saul Krugman and his group (which he has permitted me to quote), 100 infants, 2, 3, and 4 months of age, received inactivated measles virus vaccine simultaneously with DPT. Fewer than 10% of these infants acquired measles antibodies. At 12 to 14 months of age, live virus vaccine without γ-globulin was administered as a booster. Only 4 of the 100 developed fever between 102 and 103 F, and none had rash. On the other hand, when 56 other infants who had received DPT but no killed measles virus vaccine at 2, 3, and 4 months of age were given live virus at 12 to 14 months of age, fever ranging between 102 and 104 F occurred in 27%, and a modified measles rash occurred in 12.5%. The antibody response in both groups was 100%.

This, then, supports a suggestion that was made some time ago, namely, that a reasonable approach to immunization would be to combine measles with DPT in early infancy and then to use live virus vaccine as the booster in the first part of the second year of life. γ-Globulin very likely would not be needed, and the antibody response might be more substantial and of greater duration than that following "further attenuated" virus. The duration of the latter, of course, remains to be determined.

I should like now to refer briefly to some of the

data (Novack, Feldman, and Voth, *to be published*) that we have accumulated from the study we began in 1960 of the inactivated virus vaccine.

Among 794 of the children to whom we have given the vaccine, 97% were four years of age or younger. Serum was obtained from 181 (23%) before immunization was begun; 79% were serologically susceptible. Two dosage schedules had been planned. In one, each child was to receive vaccine at intervals of 1 month for a total of three doses; in the second, the first two doses were to be administered at intervals of 1 month and the third, some 5 months later. The prescribed schedules could not always be adhered to, so some variation resulted. A single lot of vaccine was used throughout the study. Unimmunized siblings were present in each household to provide maximal exposure were measles to occur in the community.

The serological conversion rates (HI antibodies) are rather interesting. Only 11% had antibodies 1 month after the first dose of vaccine, 33% were positive 1 month after the second dose, and 91%, 1 month after the third. As was observed in our original pilot study (3), the antibody levels decreased rather rapidly so that 6 to 7 months after completion of a course of vaccine essentially none was detectable in any of the children.

Measles exposure histories and sera were obtained from many of the participants in the fall of 1963. Interestingly, the sera of those in the group with positive histories of exposure had a rather high geometric mean titer of antibodies, whereas those whose histories were negative comprised a group with a very low geometric mean titer. There were some individuals in the latter group who very likely had had infections despite their negative exposure histories, because they had elevated antibody levels.

The kinds of illness reported after exposure within the household are of interest. Among those who had received only one dose of vaccine, there was a slight but definite suggestion of some modification of the resultant illness. This also had been noted previously (3). The children who had received two doses of vaccine and then were exposed reported either none or very little illness. Those who had received three doses of vaccine, however, fell into a rather interesting separation. This has been consistent and independent of the interval between the administration of the third dose of vaccine and intrafamilial exposure. Among the children who received three, monthly injections, 85% were either in the "no illness' or "mild-modified" (approximately what one might see following γ-globulin modified natural measles) categories. Unmodified measles occurred in the remaining 15%.

On the other hand, of those who had received their third dose after an interval of 4 to 10 months, 96% fell into either the "mild" or "none" categories and only 4% reported unmodified disease. Thus, the protection rate against unmodified clinical measles was 96% in this group. These may not be the best results that can be obtained, because it was found subsequently that the immunogenic capacity of the lot of vaccine employed had deteriorated over a period of months. Currently available inactivated virus vaccine appears to be more active than the material employed in the study cited.

Thus, it is apparent that whether one uses live virus vaccine with or without γ-globulin, or inactivated virus vaccine alone or followed by live virus, excellent protection against unmodified measles can be provided for a considerable period of time. Among the questions remaining to be answered is that of the duration of this solid immunity, since none of the recipients of these vaccines has been observed over a period of years. A longer interval has transpired since the live virus first was used then since the use of inactivated virus vaccine. There are some suggestions that the antibody decay rates for all methods may be more rapid than following natural measles. Consequently, the determination of the duration of immunity in the absence of reinfection with "wild" virus, both for live and inactivated virus vaccines, singly and in combination, becomes most important. Furthermore, we still may be far from having determined the optimal schedule for immunization, as witnessed by the different degrees of protection detected between our two groups.

In any event, there are available to us now several excellent alternatives for preventing measles of undiminished fury. What this means in terms of the prevention of illness and resultant sequelae is self-evident.

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